UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/539,845 | 02/09/2006 | Rudolf-Giesbert Alken | 82445 | 5014 |

23685 7590 08/05/2010

KRIEGSMAN & KRIEGSMAN
30 TURNPIKE ROAD, SUITE 9
SOUTHBOROUGH, MA 01772

| EXAMINER | |
|---|---|
| VALENROD, YEVGENY | |
| ART UNIT | PAPER NUMBER |
| 1621 | |
| MAIL DATE | DELIVERY MODE |
| 08/05/2010 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/539,845 | ALKEN, RUDOLF-GIESBERT | |
| | Examiner | Art Unit | |
| | YEVEGENY VALENROD | 1621 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-10 and 34-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-10 and 34-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

The following is a non-final rejection in application # 10/539,845.

Rejection of claims 2-6 and 34-48 under 35 USC 103(a) over Chiesi et al. is withdrawn in view of applicants' remarks.

Rejection of claims 2-5, 7-10 and 34-48 under 35 USC 103(a) is withdrawn in view of applicants' remarks.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "substantially enantiomerically pure" in claims 34-48 is a relative term which renders the claim indefinite. The term "substantially enantiomerically pure " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Particularly, it is not clear what is encompassed by the term "substantially".

The term "such as" in claims 34-41 is a relative term which renders the claim indefinite. The term "such as" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the

art would not be reasonably apprised of the scope of the invention. It is unclear if the term "such as" limits the scope of the disease to the list provided in the claims or if other, not listed disease, are included.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-6 and 41-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiesi (US 5,017,607) in view of Dyck (*Journal of Neurochemistry* **1986**, *46(2)*, pp 399 – 404), Ando et al. (US 6,603,008), Foster (US 6,221,335), Tonn et al. (*Biological Mass Spectrometry* **1993**, *22 (11)*, pp 633 – 642), Haskins (*Biomedical Spectrometry* **1982**, *9(7)*, pp 269 – 277), Wolen (*Journal of Clinical Pharmacology* **1986**; *26*, pp 419-424; abstract), Keinan et al (US 6,440,710) and Gouyette (*Biomedical And Environmental Mass Spectrometry*, **1988**, *15*, pp 243-247).

*Scope of prior art*

Chiesi teaches a method of treating Parkinson's disease and neurological syndromes connected with it by administration of the methyl ester of levodopa combined with other active ingredients including carboxylase and monoaminoxidase

inhibitors (abstract). As such the teaching of Cheisi is taken to teach both levodopa methyl ester, pharmaceutical compositions comprising levodopa and method of preparing said pharmaceutical compositions

*Difference between prior art and instant claims*

Although levodopa methyl ester of Cheisi comprises deuterium at its natural abundance, Cheisi fails to teach deuterated ester of levodopa as recited in the instant claims.

*Secondary references and obviousness argument*

First, one is motivated to prepare deuterated versions of drugs to obtain a version with better pharmaceutical properties. Advantaged attainable via deuteration of known drugs have been demonstrated throughout the art which serves as motivation for one skilled in the art to prepare deuterated versions of methyl ester of levodopa described by Chiesi.

For example, Dyck, states, "Thus, deuterium substitution seems to be a useful strategy to enhance the pharmacological effects of a compound without significantly altering its basic chemical structure" (page 399, column 1, last 5 lines),

Ando et al. teach "[S]ubstitution with heavier isotopes such as deuterium, i.e. 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances" (see col. 6, lines 59-67 and col. 7, lines 11-16).

Foster teaches that "by deuterating drugs, we have likely ... increased the lipophilic nature of the molecule" and, via the deuterium isotope effect, produced a derivative "less easily cleaved by metabolic (or destructive) processes. Hence, the elimination half life of the drug is prolonged and the drug's therapeutic effects are increased." (column 17, lines 17-32).

Second, and as an alternative branch, one is motivated to prepare deuterated versions of drugs, which can be used to obtain valuable information about how the un-deuterated drug or closely related drugs act in the body:

Tonn et al. state "Pharmacokinetic studies employing stable isotope labeled drugs... offer many advantages over the more conventional use of unlabeled drugs... A pharmacokinetic study in which a labeled and an unlabeled drug are simultaneously and independently ... is advantageous since it reduces to inter-day variability in the measured pharmacokinetic parameters. The advantages of this approach include an increase in the statistical power of the study, yielding an overall reduction in the number of study subjects, and also a diminished risk due to a reduction in the exposures to the drug. In addition, the overall time required to conduct experiments, and hence the number of samples to be collected for analysis, may also be substantially reduced." (page 633, second column). The reference study is an example of just that. Thus, one is motivated to prepare deuterated drugs to gain these explicitly set forth advantages.

Haskins, surveys the application of stable isotopes in biomedical research in several areas. For example, in stable isotope dilution assays, it notes that deuterium is "is the best heavy isotope for this work". (page 270, column 1). Also, the section on the use of stable isotopes in chronic administration studies lists only deuterium isotopes.

Wolen, noting that the lack of toxicity for deuterium makes it "ideally suited for human studies" (abstract) concludes that "the application of stable isotope methodology to the problems of bioavailability and bioequivalence have proved extremely versatile and useful. The technique is simple and powerful and results in extremely low risk to the subject." (page 423) Thus, one is motivated to prepare deuterated drugs to gain these advantages.

Keinan et al. state, "Deuterium- and tritium-labeled organic compounds have become increasingly important for the role they play in structure determination, mechanistic studies, elucidation of biosynthetic pathways and in biochemical studies." (column 1, lines 11-14)

Gouyette, gives an example with the anti-cancer drug Elliptinium. The reference notes, "New derivatives in the ellipticine series are under preclinical and clinical development. In order to study the fate of those molecules, it was decided that a standard molecule of this family of intercalating agents be labelled with stable isotopes which might be used in man without any problem of radioprotection or irradiation. Therefore, in a first step, elliptinium was labelled with three deuterium atoms, then injected intravenously into rats..." (introduction). In this way, they were "able to confirm the presence of unchanged drug in urine and in bile" and identify two metabolites. This

information provided about ellipticine is relevant to other derivatives in the ellipticine series.

These last five references are merely exemplary of the use of deuterated compounds to determine valuable information about pharmaceuticals and their analogues; there are many other such references.

Hence, it is clear that under either of these two branches, "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641, 1645.

Moreover, given that there is always a need to enhance the pharmacological effects of a compound (e.g. increased in vivo half-life) without significantly altering its basic chemical structure (first branch), or that there is always a need to reduce the time, cost, risk, and statistical imprecision of pharmacokinetic studies (e.g. measure bioavailability or identify metabolites) (second branch), and that there is only a limited number of ways that this can be done, it would be obvious to pursue a potential solution that has a reasonable expectation of success. See e.g. KSR International Co. v. Teleflex Inc., 1385, 1397; Pfizer, Inc. v. Apotex, Inc., 82 USPQ2d 1321; Alza Corp. v. Mylan Laboratories, Inc., 80 USPQ2d 1001; In re Kubin, 90 USPQ2d 1417; In re O'Farrell, 7 USPQ2d 1673, 1681; In re Eli Lilly & Co., 14 USPQ2d 1741; In re Ball Corp., 18 USPQ2d 1491.

In addition, it is clear under both branches that deuteration per se is a known improvement technique for getting a more useful version of the pharmaceutical, and that the improvement is of a predictable nature, as is seen by the success reported in the various secondary references. Thus, it would have been obvious to one of ordinary skill in the pharmaceutical art to have applied this known improvement technique in the same way to the compound of the primary reference to obtain the results reasonably predictable from the secondary references. See e.g. KSR International Co. v. Teleflex Inc., 1385, 1396; Ruiz v. AB Chance Co., 69 USPQ2d 1686; In re Nilssen, 7 USPQ2d 1500.

Accordingly the rejected claims are deemed obvious.

Some dependent claims specify various levels of deuteration. Selecting and optimizing the level of deuteration, up to an including full deuteration, would be within the skill of one seeking to achieve either of the goals set forth in the secondary references. For example, setting 100% deuteration at one position is routinely done, and as seen by the references cited above, di-deuteration and higher levels are also employed.

Claims 2-5, 7-10 and 41-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Milman et al (US 5,525,631) in view of Dyck (*Journal of*

*Neurochemistry* **1986**, *46(2)*, pp 399 – 404), Ando et al. (US 6,603,008), Foster (US 6,221,335), Tonn et al. (*Biological Mass Spectrometry* **1993**, *22 (11)*, pp 633 – 642), Haskins (*Biomedical Spectrometry* **1982**, *9(7)*, pp 269 – 277), Wolen (*Journal of Clinical Pharmacology* **1986**; *26*, pp 419-424; abstract), Keinan et al (US 6,440,710) and Gouyette (*Biomedical And Environmental Mass Spectrometry*, **1988**, *15*, pp 243-247).

*Scope of prior art*

Milman teaches a method of treating Parkinson's disease and neurological syndromes connected with it by administration of the ethyl ester of levodopa combined with other active ingredients including carboxylase and monoaminoxidase inhibitors (abstract; column 3, lines 48-55). As such the teaching of Milman is taken to teach both levodopa ethyl ester, pharmaceutical compositions comprising levodopa and method treating Parkinson's.

*Ascertaining the difference between prior art and instant claims*

Although levodopa ethyl ester of Milman comprises deuterium at its natural abundance, Milman fails to teach deuterated ester of levodopa as recited in the instant claims.

*Secondary references and obviousness argument*

First, one is motivated to prepare deuterated versions of drugs to obtain a version with better pharmaceutical properties. Advantaged attainable via deuteration of

known drugs have been demonstrated throughout the art which serves as motivation for one skilled in the art to prepare deuterated versions of ethyl ester of levodopa described by Milman.

For example, Dyck, states, "Thus, deuterium substitution seems to be a useful strategy to enhance the pharmacological effects of a compound without significantly altering its basic chemical structure" (page 399, column 1, last 5 lines),

Ando et al. teach "[S]ubstitution with heavier isotopes such as deuterium, i.e. 2H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements and, hence, may be preferred in some circumstances" (see col. 6, lines 59-67 and col. 7, lines 11-16).

Foster teaches that "by deuterating drugs, we have likely ... increased the lipophilic nature of the molecule" and, via the deuterium isotope effect, produced a derivative "less easily cleaved by metabolic (or destructive) processes. Hence, the elimination half life of the drug is prolonged and the drug's therapeutic effects are increased." (column 17, lines 17-32).

Second, and as an alternative branch, one is motivated to prepare deuterated versions of drugs, which can be used to obtain valuable information about how the un-deuterated drug or closely related drugs act in the body:

Tonn et al. state "Pharmacokinetic studies employing stable isotope labeled drugs... offer many advantages over the more conventional use of unlabeled drugs... A

pharmacokinetic study in which a labeled and an unlabeled drug are simultaneously and independently ... is advantageous since it reduces to inter-day variability in the measured pharmacokinetic parameters. The advantages of this approach include an increase in the statistical power of the study, yielding an overall reduction in the number of study subjects, and also a diminished risk due to a reduction in the exposures to the drug. In addition, the overall time required to conduct experiments, and hence the number of samples to be collected for analysis, may also be substantially reduced." (page 633, second column). The reference study is an example of just that. Thus, one is motivated to prepare deuterated drugs to gain these explicitly set forth advantages.

Haskins, surveys the application of stable isotopes in biomedical research in several areas. For example, in stable isotope dilution assays, it notes that deuterium is "is the best heavy isotope for this work". (page 270, column 1). Also, the section on the use of stable isotopes in chronic administration studies lists only deuterium isotopes.

Wolen, noting that the lack of toxicity for deuterium makes it "ideally suited for human studies" (abstract) concludes that "the application of stable isotope methodology to the problems of bioavailability and bioequivalence have proved extremely versatile and useful. The technique is simple and powerful and results in extremely low risk to the subject." (page 423) Thus, one is motivated to prepare deuterated drugs to gain these advantages.

Keinan et al. state, "Deuterium- and tritium-labeled organic compounds have become increasingly important for the role they play in structure determination,

mechanistic studies, elucidation of biosynthetic pathways and in biochemical studies." (column 1, lines 11-14)

Gouyette, gives an example with the anti-cancer drug Elliptinium. The reference notes, "New derivatives in the ellipticine series are under preclinical and clinical development. In order to study the fate of those molecules, it was decided that a standard molecule of this family of intercalating agents be labelled with stable isotopes which might be used in man without any problem of radioprotection or irradiation. Therefore, in a first step, elliptinium was labelled with three deuterium atoms, then injected intravenously into rats..." (introduction). In this way, they were "able to confirm the presence of unchanged drug in urine and in bile" and identify two metabolites. This information provided about ellipticine is relevant to other derivatives in the ellipticine series.

These last five references are merely exemplary of the use of deuterated compounds to determine valuable information about pharmaceuticals and their analogues; there are many other such references.

Hence, it is clear that under either of these two branches, "a person of ordinary skill in the art would have been motivated to combine the prior art to achieve the claimed invention and that there would have been a reasonable expectation of success." DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 80 USPQ2d 1641, 1645.

Moreover, given that there is always a need to enhance the pharmacological effects of a compound (e.g. increased in vivo half-life) without significantly altering its basic chemical structure (first branch), or that there is always a need to reduce the time, cost, risk, and statistical imprecision of pharmacokinetic studies (e.g. measure bioavailability or identify metabolites) (second branch), and that there is only a limited number of ways that this can be done, it would be obvious to pursue a potential solution that has a reasonable expectation of success. See e.g. KSR International Co. v. Teleflex Inc., 1385, 1397; Pfizer, Inc. v. Apotex, Inc., 82 USPQ2d 1321; Alza Corp. v. Mylan Laboratories, Inc., 80 USPQ2d 1001; In re Kubin, 90 USPQ2d 1417; In re O'Farrell, 7 USPQ2d 1673, 1681; In re Eli Lilly & Co., 14 USPQ2d 1741; In re Ball Corp., 18 USPQ2d 1491.

In addition, it is clear under both branches that deuteration per se is a known improvement technique for getting a more useful version of the pharmaceutical, and that the improvement is of a predictable nature, as is seen by the success reported in the various secondary references. Thus, it would have been obvious to one of ordinary skill in the pharmaceutical art to have applied this known improvement technique in the same way to the compound of the primary reference to obtain the results reasonably predictable from the secondary references. See e.g. KSR International Co. v. Teleflex Inc., 1385, 1396; Ruiz v. AB Chance Co., 69 USPQ2d 1686; In re Nilssen, 7 USPQ2d 1500.

Accordingly the rejected claims are deemed obvious.

Some dependent claims specify various levels of deuteration. Selecting and optimizing the level of deuteration, up to an including full deuteration, would be within the skill of one seeking to achieve either of the goals set forth in the secondary references. For example, setting 100% deuteration at one position is routinely done, and as seen by the references cited above, di-deuteration and higher levels are also employed.

***Reply to applicants' remarks regarding the obviousness rejections***

In the remarks filed 3/5/10 applicants have argued that the Dewar et al. reference supports applicants' position that one skilled in the art would not expect an improvement in properties when the compounds of Milman and Chieti are deuterated. In support of this argument applicants have indicated that when Dewar made deuterated version of racemic DL-DOPA no statistical difference between deuterated and non-deuterated DL-DOPA was observed.

This argument is not found persuasive. It is well known in the art that a racemic pharmaceutical and enantiomerically pure pharmaceutical can often have drastically different physiological effect and mechanism of action. A very well known example of this is the sedative drug thalidomide, which was withdrawn from the market in 1961 when it was discovered that the racemic mixture results in birth defects and only one of the stereoisomers was responsible for the desired pharmacological effect. One skilled in the art is well aware of the difference in the pharmacological effect when a pure

stereoisomer is compared to a racemic mixture or to the opposite stereoisomer. As such one would not be discouraged by the results of Dewar. One would still find it obvious to prepare deuterated versions of the L-DOPA derivatives taught by Milman and Chieti for the reasons described above. Regarding 3,4-dihydroxyphenylalanine (DOPA), it has been shown that the L and D isomers are metabolized differently and result in different urine dopamine concentration, which supports the argument that one skilled in the art would not draw conclusions regarding deuteration of L-DOPA derivatives, based on the experimental data presented by Dewar et al. (Sourkes et al. *Biochem. J.* **1964**, *93*, pages 469-474).

***Conclusion***

Claims 2-10 and 34-48 are pending

Claims 2-10 and 34-48 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yevgeny Valenrod whose telephone number is 571-272-9049. The examiner can normally be reached on 8:30am-5:00pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Yevgeny Valenrod/

Yevgeny Valenrod
Patent Examiner
Technology Center 1600